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High Dose Oral Amiodarone Loading: Electrophysiologic Effects and Clinical Tolerance

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Although amiodarone is an effective drug for the treatment of life-threatening ventricular arrhythmias, no standard oral loading dose protocol has been defined, and patients often undergo prolonged hospitalization for amiodarone loading. High dose (>1,800 mg/day) oral loading has usually been reserved for unstable patients with incessant ventricular tachyarrhythmias. The current study was designed to 1) examine the clinical and electrophysiologic effects of a high dose oral amiodarone loading regimen in more stable patients; and 2) ascertain its safety and tolerance, possibly allowing shortened amiodarone loading periods and potentially decreased length of hospital stay.

The study group included 16 patients with a history of recurrent ventricular arrhythmias and decreased left ventricular function, who were refractory to prior antiarrhythmic drug therapy. The oral loading protocol was 50 mg/kg per day of amiodarone for 3 days, then 30 mg/kg per day for 2 days, followed by maintenance therapy of 300 to 400 mg twice daily. Electrophysiologic testing was performed at baseline, on days 1 and 5 and during week 6. Amiodarone and desethylamiodarone levels were measured and symptoms monitored.

Clinically, the high dose loading protocol was well tolerated in 15 of the 16 patients. Arrhythmias were rendered noninducible by day 1 in three patients and remained noninducible throughout the study period in two of the three. The remaining patients continued to have inducible ventricular tachycardia. Ventricular tachycardia cycle length and right ventricular effective refractory period both progressively increased significantly over baseline, starting on day 1. The 15 patients who remained in the study had no significant side effects during the loading period. Eleven patients have been followed up for >2 years without any clinical recurrence of their presenting arrhythmia.

High dose oral amiodarone loading is clinically well tolerated in patients with life-threatening ventricular arrhythmias who have depressed ventricular function. This regimen may allow decreased loading periods, thereby permitting shorter hospital stays in this patient population.

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Amiodarone is an effective drug for the therapy of life-threatening ventricular arrhythmias (1), but treatment protocols are not standardized in terms of loading dosage, length of loading period or maintenance dosage. Loading doses of 400 to 1,800 mg/day of amiodarone for 1 to 6 weeks, followed by variable maintenance doses of 200 to 800 mg/day, have been reported to be effective in suppressing ventricular arrhythmias and improving survival (2–6). High loading doses (>800 mg/day) have in general been avoided, predominantly because of concern for precipitation of acute side effects, such as severe exacerbation of congestive heart failure and proarrhythmia. However, two groups using oral amiodarone loading doses of up to 4.4 g/day have reported rapid suppression of spontaneous severe complex ventricular arrhythmias (7,8). In addition, these dosages were clinically well tolerated.

The selection of the appropriate loading dose regimen still poses a major challenge to clinicians because of amiodarone's unusual pharmacokinetic properties. It is a very lipophilic drug with a half-life of up to 40 days, whose major metabolite, desethylamiodarone, has an even longer half-life than its parent compound (9). The antiarrhythmic properties of amiodarone may be manifested before total body tissue equilibration has occurred, and desethylamiodarone may contribute to the overall long-term antiarrhythmic effects (10).

The uncertainties with regard to the short-term administration of amiodarone are clinically significant. High dose oral amiodarone loading has been previously studied in patients with incessant ventricular arrhythmias (8), a group that comprises a relatively small proportion of the total

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population of patients with life-threatening ventricular arrhythmias. The present study was undertaken in patients with a history of life-threatening ventricular arrhythmias and depressed ventricular function who do not have incessant ventricular arrhythmias. The aims were 1) to determine the clinical tolerance of a high dose oral amiodarone loading regimen in such patients; 2) to examine the electrophysiologic effects of such a high dose regimen both immediately and at 6 weeks; 3) to ascertain whether such a regimen could potentially be used to decrease the length of time of amiodarone loading in this patient group; and 4) to observe the outcome during long-term follow-up.

Methods

Patients. Sixteen patients were initially entered into the study. One patient, with a diagnosis of left ventricular aneurysm secondary to myocardial infarction, congestive heart failure and an ejection fraction of 12%, had an exacerbation of congestive heart failure after the first loading dose. Although successfully treated with increased doses of diuretics, he was withdrawn from the study at the request of his physician and started on a regimen of lower doses of amiodarone. No follow-up electrophysiologic testing was performed in this patient. Thus, the study group included 15 patients (Table 1) with a history of recurrent ventricular tachycardia who had undergone a mean of 2.7 prior unsuccessful trials of antiarrhythmic drugs. The average age was 64 years, and the average ejection fraction was 29%. The underlying etiology was ischemic heart disease in all patients. No patient had had a myocardial infarction within the month preceding the study. All patients had inducible sustained ventricular tachycardia, but no patient had incessant ventricular arrhythmias.

Electrophysiologic testing protocol. After informed consent was obtained, electrophysiologic testing was performed with the patient in the postabsorptive state. All antiarrhythmic therapy was discontinued for at least 5 half-lives before the baseline electrophysiologic study was performed. The details of our stimulation protocol have been reported previously (11). A new catheter was placed for each study, and the same protocol followed. Ventricular tachycardia cycle length, right ventricular effective refractory period at a pacing cycle length of 550 ms and two times diastolic threshold, number of extrastimuli required to induce ventricular tachycardia, ventricular tachycardia configuration, method of tachycardia termination, and symptoms during ventricular tachycardia were carefully recorded.

Amiodarone loading. The dosing protocol was based on prior high dose loading regimens (7,8): 50 mg/kg body weight per day of oral amiodarone was given on days 1 through 3, and 30 mg/kg per day on days 4 and 5, after baseline electrophysiologic testing. This protocol resulted in the administration of 3 to 5.2 g/day of amiodarone for the 1st 3 days, and of 1.7 to 3.1 g/day on days 4 and 5. Maintenance dosing was then instituted at 300 to 400 mg twice daily. Repeat electrophysiologic studies were performed on days 1 and 5 and at week 6. Symptoms were closely monitored during the loading phase, and plasma levels of amiodarone and desethylamiodarone were measured at the time of the repeat electrophysiologic studies (whether or not this time represented the interdosage trough point).

Results

Electrophysiologic variables. All 15 patients who tolerated the full high dose loading protocol underwent electrophysiologic testing at baseline and on days 1 and 5; 13 patients had follow-up electrophysiologic testing at week 6 (1 moved away, 1 refused further follow-up). The mean total dose of amiodarone by day 5 was 11.9 g (Table 1). Clinical and electrophysiologic changes were observed to start at day 1 (Table 2). At baseline, all 15 patients had inducible, sustained ventricular tachycardia. By day 1, ventricular tachycardia was not inducible in two patients and only nonsustained ventricular tachycardia was inducible in one patient. At day 5, ventricular tachycardia remained noninducible in the two patients who had noninducible arrhythmia on day 1 (one had ventricular fibrillation that was considered to be a nonclinical, rather than a proarrhythmic response); however, the patient with nonsustained ventricular tachycardia again had sustained ventricular tachycardia. At the 6 week follow-up, one of the patients with previously inducible arrhythmia crossed over into the group with noninducible arrhythmia (nonsustained ventricular tachycardia), and arrhythmia continued to be noninducible in the two patients with previously noninducible arrhythmia (with the same patient having nonclinical ventricular fibrillation).

The ventricular tachycardia cycle length at baseline was 259 ± 64 ms (Table 2); by day 1, it had increased significantly to 315 ± 101 ms ($p < 0.05$ from day 1). At day 5, there was no significant increase over baseline or day 1 in the ventricular tachycardia cycle length, but by week 6 the cycle length had increased significantly to 373 ± 66 ms from day 1 and day 5 ($p < 0.05$ vs. baseline, day 1 and day 5). The right ventricular effective refractory period followed a similar pattern initially. The baseline right ventricular effective refractory period was 252 ± 22 ms (Table 2), which increased significantly to 279 ± 17 ms on day 1 ($p < 0.05$). On day 5 there was no significant increase over baseline or day 1 in the right ventricular effective refractory period, but by week 6 it had significantly increased from day 1 to 307 ± 22 ms ($p < 0.05$ vs. baseline and day 1). There was no consistent change in number of extrastimuli necessary to induce ventricular tachycardia associated with the increases in ventricular tachycardia cycle length and right ventricular effective refractory period. Seven patients had the same and six patients had a different ventricular tachycardia configuration after receiving amiodarone, but there was no significant difference in the increase in ventricular tachycardia cycle length between the two groups. There was also no consistent change in the symptoms reported during the

Table 1. Clinical Characteristics and Cumulative Amiodarone Dose on Day 5 in 15 Patients

Pt. No.	Age (yr)/ Gender	Diagnosis	Symptoms During VT/VF	Prior Drug Trials	EF(%)	Cumulative Amiodarone Dose On Day 5 (g)
1	78/M	MI,LVH,CHF	Hypotens	3	3[illegible]	11.6
2	45/M	MI,CABG	SCD	3	2[illegible]	12.6
3	61/M	MI	Chest pain	3	1[illegible]	11.6
4	67/F	MI,CABG	Dizziness	3	[illegible]	11.6
5	72/F	MI	Syncope	2	2[illegible]	12.0
6	59/M	MI	Syncope	2	2[illegible]	14.6
7	69/M	MI,CABG	Syncope	3	1[illegible]	13.3
8	73/M	MI,LVA	Syncope	2	22	11.5
9	66/M	MI	SCD	3	44	13.8
10	74/M	MI,LVA	SCD	3	20	11.2
11	37/M	MI,LVA	Syncope	2	20	13.6
12	61/F	MI	SCD	3	37	10.8
13	67/M	MI,CABG,LVA	Syncope	3	16	9.8
14	78/M	MI	Syncope	3	31	10.7
15	67/M	MI	Dizziness	3	35	10
Mean	6[illegible]			2.75	29%	11.9
SD	1[illegible]			0.5	10%	1.4

All values are mean values ± SD. CABG = coronary artery bypass surgery; CHF = congestive heart failure; EF = ejection fraction; F = female; Hypotens = symptomatic hypotension; LVA = left ventricular aneurysm; M = male; MI = myocardial infarction; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.

ventricular tachycardia or in the method of tachycardia termination.

Plasma amiodarone and desethylamiodarone levels. Plasma amiodarone levels were 2.6 ± 1 mg/liter on day 1 (Table 2). There was no further significant change by day 5 or week 6. Desethylamiodarone levels were 0.4 ± 0.2 mg/liter on day 1 (Table 2). However, by day 5, the levels had risen significantly over day 1 values to 0.6 ± 0.2 mg/liter ($p < 0.05$) and by week 6 had increased further to 1.1 ± 0.3 mg/liter ($p < 0.05$ vs. day 1 and day 5).

Side effects. One patient, with a left ventricular ejection fraction of 12%, was withdrawn from the loading protocol because of an exacerbation of congestive heart failure. The remaining 15 patients included in the study had no cardiovascular, neurologic or gastrointestinal symptoms during the loading period. At 6 week follow-up, three patients had developed new symptoms (tremor, insomnia and new congestive heart failure in one patient receiving 600 mg/day; slight incoordination and mild nausea in a patient receiving 800 mg/day and paresthesias and headache in a patient receiving 800 mg/day). One patient was admitted to the hospital 1 month after the week 6 follow-up electrophysiologic study with a non Q wave myocardial infarction and ventricular tachycardia of two different configurations from that seen during the testing period; he underwent successful cardioversion.

Discussion

High dose oral amiodarone loading was clinically well tolerated in 15 of 16 patients with depressed ventricular function and life-threatening ventricular arrhythmias. Electrophysiologic changes were noted by day 1, and continued changes in the electrophysiologic variables were observed through week 6. Follow-up revealed good long-term survival.

Table 2. Electrophysiologic Findings and Amiodarone and Desethylamiodarone Levels in the 15 Study Patients

Variable	Baseline	Day 1	Day 5	Week 6
% of patients with inducible VT/VF	100% [15]	80% [15]	93% [15]	85% [13]
VTCL (ms)	259 ± 64 [15]	315 ± 101* [12]	340 ± 134* [13]	373 ± 66*† [10]
RVERP (ms)	252 ± 22 [14]	279 ± 17* [15]	303 ± 36* [14]	307 ± 22*† [13]
Plasma amiodarone level (mg/liter)		2.6 ± 1 [15]	2.6 ± 0.6 [14]	2.1 ± 0.8 [13]
Plasma desethylamiodarone level (mg/liter)		0.4 ± 0.2 [15]	0.6 ± 0.2* [15]	1.1 ± 3†‡ [13]

*, †, ‡ = $p < 0.05$ versus baseline (*), day 1 (†) or day 5 (‡). p Values were obtained by paired t test using the Bonferroni correction for multiple comparisons. Unless otherwise indicated, all values are mean values ± SD. The numbers in brackets indicate the number of patients (from the total cohort of 15) with the measured variable. RVERP = right ventricular effective refractory period; VF = ventricular fibrillation; VT = ventricular tachycardia; VTCL = ventricular tachycardia cycle length.

Clinical tolerance. Few studies are available documenting the short-term effects of high dose oral amiodarone loading (7,8). Apart from the one patient who was withdrawn from the study because of symptomatic congestive heart failure after the first loading dose, no patient experienced symptoms of drug toxicity during the loading period. This observation reveals that, even in patients with markedly depressed left ventricular function, high dose loading is unlikely to cause significant hemodynamic compromise. Hence, when urgent amiodarone loading is not required, this regimen may be safer than rapid intravenous amiodarone loading, which may result in hemodynamic compromise (12).

Although not universally accepted, significant positive correlations between plasma amiodarone levels and toxicity have been previously reported (3,13). The paucity of symptoms in our patient group during the acute loading phase may therefore relate to a nontoxic range of their serum amiodarone concentrations during the loading period. Not unexpectedly, several patients did experience minor symptoms reported at the 6-week follow-up period, and the maintenance dose of amiodarone was readjusted at that point.

Electrophysiologic effects. The increases in ventricular tachycardia cycle length and right ventricular effective refractory period seen in our patients are similar to those reported previously (2,3,10,14–17) with lower dose loading protocols and electrophysiologic testing performed 1 to 20 weeks after the initiation of amiodarone therapy. With the loading protocol used in our study, significant prolongations of the ventricular tachycardia cycle length and right ventricular effective refractory period were already noted by day 1.

Although still controversial, evidence suggests that electrophysiologic testing may be advantageous to predict the long-term outcome of amiodarone therapy (17–21). Reported positive prognostic indicators obtained during electrophysiologic testing after amiodarone loading have included complete suppression of arrhythmia inducibility (19,20), a change from inducible sustained ventricular tachycardia to nonsustained ventricular tachycardia (17), improved hemodynamic tolerance of the induced arrhythmia (14) and an increase in the cycle length of the induced ventricular tachycardia (21). Although early significant changes were seen in the ventricular tachycardia cycle length and right ventricular effective refractory period in our study, tachycardia remained inducible in most patients, and there were no significant changes in hemodynamic tolerance of the ventricular tachycardia.

The reasons for the disparity between the electrophysiologic effects of amiodarone and its clinical efficacy are unknown, but several groups, including ours, have reported similar findings (2,3,14,15). Hence, although noninducibility of arrhythmia after amiodarone therapy may be a helpful prognostic indicator (19,22), treatment with amiodarone may confer significant protection from arrhythmia recurrence and sudden cardiac death despite persistent inducibility (14,15).

Amiodarone levels. The amiodarone levels achieved within the 1st 24 h of the study were similar to those reported by Mostow et al. (8), whose patients received up to 4.4 g of amiodarone daily. The electrophysiologic effects of amiodarone were also noted to be significant within this period. It has been shown that there are measurable tissue amiodarone levels after a single oral (7) or intravenous (23) dose, a time when desethylamiodarone levels are absent or low. Hence, it is likely that amiodarone itself has electrophysiologic effects independent of those of desethylamiodarone, and contributes to the overall antiarrhythmic properties of the drug (24).

Although the amiodarone levels remained stable over the follow-up period, the desethylamiodarone levels continued to rise, in conjunction with a continued increase in the ventricular tachycardia cycle length and right ventricular effective refractory period. Similar results were reported by Mitchell et al. (10). It has been postulated that desethylamiodarone contributes to the antiarrhythmic effects of amiodarone (10,24,25). Therefore, the further increases in the electrophysiologic variables may have been in part related to the higher desethylamiodarone levels, as well as to the equilibration of amiodarone and desethylamiodarone throughout all body tissues (23).

Several groups have examined the relation between amiodarone levels and inducibility of ventricular tachycardia at electrophysiologic study. No correlation has been observed between plasma concentration of amiodarone or desethylamiodarone and inducibility of ventricular tachycardia at electrophysiologic study (3,22), number of extrastimuli required for induction (26) of ventricular tachycardia or clinical recurrence of ventricular arrhythmias (3,22). This suggests that although the electrophysiologic effects of amiodarone are related to the plasma levels of amiodarone and desethylamiodarone, monitoring of plasma levels in addition to electrophysiologic study is not helpful in predicting the arrhythmia recurrence.

Long-term follow-up. The patient initially excluded from the study was not followed up. In addition, two patients were lost to follow-up (one moved away, one refused further follow-up). Two patients died of nonarrhythmic causes within 6 months of their 6-week follow-up electrophysiologic study (one of intractable congestive heart failure and one of metastatic carcinoma). The remaining 11 patients have all been followed up for >2 years without clinical recurrence of their presenting arrhythmia. One patient received an implantable defibrillator. Amiodarone was discontinued in one patient because of visual side effects thought to be secondary to amiodarone, and mexilitene was substituted. Ten of the 15 patients continue to receive amiodarone. The clinical tolerance of amiodarone in the present study compares favorably with results reported recently in two long-term follow-up studies of much larger numbers of patients both at this institution (27) and elsewhere (28).

Conclusions. The present study has shown that the use of a high dose loading regimen of amiodarone is clinically well tolerated in patients with life-threatening ventricular arrhythmias and depressed ventricular function. Furthermore, the electrophysiologic effects of amiodarone are manifested

early during high dose loading and may be due to the parent drug. The further changes observed with time in electrophysiologic variables, despite stable amiodarone plasma levels, suggest an additional effect of desethylamiodarone. Despite persistent arrhythmia inducibility, long-term follow-up of these patients shows a survival rate similar to that of patients who have received lower dose loading regimens.

Although there is a small potential to exacerbate preexisting depressed left ventricular function, the use of a high dose oral amiodarone loading regimen appears to be clinically safe. Because of its clinical safety and good tolerance, high dose oral amiodarone loading may permit shorter loading periods, thereby allowing a shorter hospital stay for patients who require amiodarone therapy for life-threatening ventricular arrhythmias. Further studies with larger numbers of patients are warranted to determine the best high dose oral loading regimen.

References

1. Zipes DZ, Prystowsky EN, Heger JJ. Amiodarone: electrophysiologic actions, pharmacokinetics, and clinical effects. J Am Coll Cardiol 1984; 3:1059–71.
2. Kennedy EE, Rosenfeld LE, McPherson CA, Batsford WP. Evaluation by serial electrophysiologic studies of an abbreviated oral loading regimen of amiodarone. Am J Cardiol 1985;55:867–71.
3. Greenberg ML, Lerman BB, Shipe JR, Kaiser DL, DiMarco JP. Relation between amiodarone and desethylamiodarone plasma concentrations and electrophysiologic effects, efficacy, and toxicity. J Am Coll Cardiol 1987;9:1148–55.
4. Peter T, Hamer A, Weiss D, Mandel WJ. Prognosis after sudden cardiac death without associated myocardial infarction: one year follow-up of empiric therapy with amiodarone. Am Heart J 1984;107:209–15.
5. Haffajee CI, Love JC, Alpert JS, Asdourian GK, Sloan KC. Efficacy and safety of long-term amiodarone in treatment of cardiac arrhythmias: dosage experience. Am Heart J 1983;106:935–43.
6. Heger JJ, Prystowsky EN, Zipes DP. Clinical efficacy of amiodarone in treatment of recurrent ventricular tachycardia and ventricular fibrillation. Am Heart J 1983;106:887–94.
7. Escoubet B, Counel P, Poirier JM, et al. Suppression of arrhythmias within hours after a single oral dose of amiodarone and relation to plasma and myocardial concentrations. Am J Cardiol 1985;55:696–702.
8. Mostow ND, Vrobel TR, Noon D, Kalita L. Rapid suppression of complex ventricular arrhythmias with high dose oral amiodarone. Circulation 1986;73:123–6.
9. Holt DW, Tucker GT, Jackson PR, Storey GCA. Amiodarone pharmacokinetics. Am Heart J 1983;106:840–7.
10. Mitchell LB, Wyse G, Gillis AM, Duff HJ. Electropharmacology of amiodarone therapy initiation: time courses of onset of electrophysiologic and antiarrhythmic effects. Circulation 80:1989:34–42.
11. Oseran DS, Gang ES, Hamer AW, et al. Mode of stimulation versus response: validation of a protocol for induction of ventricular tachycardia. Am Heart J 1985;110:646–51.
12. Marcus FI, Fontaine GH, Frank R, et al. Clinical pharmacology and therapeutic applications of the antiarrhythmic agent, amiodarone. Am Heart J 1981;101:480–93.
13. Haffajee CL, Love JC, Canada AT, Lesko LJ, Asdourian G, Alpert JS. Clinical pharmacokinetics and efficacy of amiodarone for refractory tachyarrhythmias. Circulation 1983;67:1347–55.
14. Kadish AH, Buxton AE, Waxman HL, Flores B, Josephson ME, Marchlinski FE. Usefulness of electrophysiologic study to determine the clinical tolerance of arrhythmia recurrences during amiodarone therapy. J Am Coll Cardiol 1987;10:90–6.
15. Hamer AW, Finerman WB, Peter T, Mandel WJ. Disparity between the clinical and electrophysiologic effects of amiodarone in the treatment of recurrent ventricular tachyarrhythmias. Am Heart J 1981;102:992–1000.
16. Nademanee K, Hendrickson J, Kannan R, Singh BN. Antiarrhythmic efficacy and electrophysiologic actions of amiodarone in patients with life-threatening ventricular arrhythmias: potent suppression of spontaneously occurring tachyarrhythmias vs. susinconsistent abolition of induced ventricular tachycardia. Am Heart J 1982;103:950–9.
17. Manolis AS, Uricchio F, Estes NAM III: Prognostic value of early electrophysiologic studies for ventricular tachycardia recurrence in patients with coronary artery disease treated with amiodarone. Am J Cardiol 1988;63:1052–7.
18. Horowitz LN, Spielman SR, Greenspan AM, Webb CR, Kay HR. Ventricular arrhythmias: use of electrophysiologic studies. Am Heart J 1983;106:881–6.
19. Lavery D, Saksena S. Management of refractory sustained ventricular tachycardia with amiodarone: a reappraisal. Am Heart J 1987;113:49–56.
20. McGovern B, Garan H, Malacoff RF, et al. Long-term clinical outcome of ventricular tachycardia or fibrillation treated with amiodarone. Am J Cardiol 1984;53:1558–63.
21. Yazaki Y, Haffajee CL, Gold RL, Bishop RL, Alpert JS. Electrophysiologic predictors of long-term clinical outcome with amiodarone for refractory ventricular tachycardia secondary to coronary artery disease. Am J Cardiol 1987;60:293–7.
22. Horowitz LN, Spielman SR, Greenspan AM, et al. Usefulness of electrophysiologic testing in evaluation of amiodarone therapy for sustained ventricular tachyarrhythmias associated with coronary heart disease. Am J Cardiol 1985;55:367–71.
23. Talajic M, DeRoode MR, Nattel S. Comparative electrophysiologic effects of intravenous amiodarone and desethylamiodarone in dogs: evidence for clinically relevant activity of the metabolite. Circulation 1987;75:265–71.
24. Heger JJ, Prystowsky EN, Zipes DP. Relationships between amiodarone dosage, drug concentrations, and adverse side effects. Am Heart J 1983;106:934–5.
25. Latini R, Connolly SJ, Kates RE. Myocardial disposition of amiodarone in the dog. J Pharmacol Exp Ther 1983;224:603–8.
26. DiCarlo LA, Morady F, deBuitlier M, Baerman JM, Schurig L, Annesley T. Effects of chronic amiodarone therapy on ventricular tachycardia induced by programmed ventricular stimulation. Am Heart J 1987;113: 57–64.
27. Myers M, Peter CT, Weiss D, et al. Benefit and risks of long-term amiodarone therapy for sustained ventricular tachycardia/fibrillation: minimum of three-year follow-up in 145 patients. Am Heart J 1990;119: 8–14.
28. Herre JM, Sauve MJ, Malone P, et al. Long-term results of amiodarone therapy in patients with recurrent sustained ventricular tachycardia or ventricular fibrillation. J Am Coll Cardiol 1989;13:442–9.